Effect of Semipermeable Coating Composition and Opadry® Top-Coating Systems on Performance of Push-Pull Osmotic Pump Tablets of a Practically Water Insoluble Model Drug

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Purpose

There has been increasing interest in the development of oral osmotic dosage forms in which drugs can be delivered at a constant rate (zero order release) over a long period of time. Drug release from osmotic dosage forms is generally independent of pH, ionic strength, agitation and other physiological factors within the gastrointestinal tract. These attributes minimize patient-to-patient variability and allow accurate prediction of in vivo performance from in vitro dissolution profiles. However, access to the technologies has been restricted due to the perceived complexity of these formulations, manufacturing challenges and patent landscape.[1, 2]

In this study, push-pull osmotic pumps (PPOP) of a practically insoluble model drug (Drug Y) were developed using the formulation strategy as described previously.[3] The objective of this study is twofold: (i) to investigate the effect of the semipermeable coating composition comprising cellulose acetate along with different grades of polyethylene glycol (PEG); and (ii) to evaluate the effect of various Opadry film coating systems, on performance of the developed PPOPs. These investigations could lead to better understanding of the robustness of the PPOP tablets and designing studies to assess process variable impact, as prescribed in ICH 8, Pharmaceutical Development.

Methods

Effect of semipermeable coating composition using various grades of PEG

In PPOP tablets, the semipermeable membrane acts as a barrier to control the diffusion of water into the tablet core and the drug delivery out of the pump. The membrane is generally composed of cellulose acetate as a water insoluble, film forming polymer in combination with polyethylene glycol (PEG) as a plasticizer and pore former.[1] The common grades of cellulose acetate and PEG are CA-398-10 and PEG 3350.

In this study, the effect of PEG grades of lower and higher molecular weight, i.e. PEG 400 and PEG 8000, was also evaluated. For this evaluation, tablet cores were prepared as described elsewhere.[4] Briefly, the pull and push layer formulations (**Table 1**) were prepared using a hydro-alcoholic high shear granulation process (batch size, 1 kg). Bilayer tablets were prepared on a rotary press (Piccola, Riva, Argentina) using standard round concave tooling (9.5 mm) at the target weight of 330 mg. A tamping force (pressure) of ~0.7 kN (9.8 MPa) was used to compress the pull layer, followed by main compression force (pressure) of 7 kN (98 MPa) to compress the bilayer tablets. The resulting tablets were coated to 8-12% w/w weight gain (WG) of a semipermeable membrane (**Table 2**).

The coating solution was prepared by dissolving PEG in water followed by addition of this solution to acetone. Cellulose acetate was then added to the above mixture and stirred to achieve a clear solution. The coating process was performed in a Vector Hi-Coater LDCS (batch size, 1.5 kg, with inclusion of placebo tablets) at a product temperature of 28ºC. Coated tablets were dried in a vacuum drying oven at 40ºC for 24 hours to remove residual solvent and moisture.

A delivery orifice was drilled on the drug layer side of the coated tablets using a laser machine (Cobalt 250, InkCupsNow, USA). Tablets were evaluated for physical properties and in vitro drug release based on the USP methods. Drug release profiles were compared using similarity factors ($f2$).[5]

Table 1. Formulation of Pull and Push Layers for PPOP Tablets of Model Drug Y

Pull Layer Ingredients	Supplier	Quantity (%w/w)
Drug Y	-	5.6
Polyethylene oxide (POLYOX™ WSR N-80)	The Dow Chemical Company, USA	93.9
Magnesium stearate	Mallinckrodt, USA	0.5
Total		**100**
Push Layer Ingredients	**Supplier**	**Quantity (%w/w)**
Polyethylene oxide (POLYOX™ WSR Coagulant)	The Dow Chemical Company, USA	64.0
Sodium chloride	Mallinckrodt, USA	35.0
Pigment, red iron oxide	Rockwood Pigments, Italy	0.5
Magnesium stearate	Mallinckrodt, USA	0.5
Total		**100**

Table 2. Semipermeable Coating Composition

Ingredients	Supplier	Quantity (%w/w)
Cellulose acetate, CA-398-10	Eastman Chemical Company, USA	6.3
PEG (400 or 3350 or 8000)	The Dow Chemical Company, USA	0.7
Acetone	Spectrum Chemical, USA	89
Deionized water	-	4
Total		**100**

Effect of Various Opadry Top-Coating Systems

Commercially available PPOP tablets are often film coated in order to effectively mask the bilayer appearance through the semipermeable coating. Coating also covers the delivery orifice to the extent possible for dose differentiation and branding, and to provide a high quality finish for aesthetic purposes and printing applications (**Figure 1**).

To evaluate the effect of top-coating on drug release, the PPOP tablets, coated with cellulose acetate and PEG 3350 to 12% weight gain, were coated with various white Opadry systems of different chemistries, HPMC-based and PVA-based systems, i.e. YS-2-7063, 85F18422 and 89F18626. Tablets were top-coated in a fully perforated coating pan (Labcoat I, O'Hara, Canada) (batch size, 1 kg) using the recommended coating process parameters for each system. Top-coated tablets of each Opadry system with 3% and 6% weight gain were evaluated for in vitro drug release based on the USP methods. Drug release profiles were compared for similarity using the PPOP tablets without the Opadry top-coat as reference.

Results

Evaluation of physical properties of the uncoated bilayer tablets (**Table 3**) showed that these tablets had sufficient mechanical strength and hence were suitable for coating application.

Table 3. Physical Properties of the Uncoated Bilayer Tablets

Parameters	Tablets
Tablet weight (mg)	332 ± 4.1
Tablet thickness (mm)	5.03 ± 0.05
Tablet hardness (kp) (Tensile strength (MPa))	9.4 ± 1.2 (1.36)
Tablet friability (%)	0.0

The lag time for all systems was about 2 hours and independent of PEG MW. Drug release for PEG 400 and 3350 was similar ($f2$>75), while using PEG 8000 led to slightly slower drug release ($f2$<50) (**Figure 2**). This could be attributed to the slightly lower aqueous solubility of PEG 8000.

Application of Opadry coating systems resulted in tablets with smooth surfaces and similar drug release profiles compared to the PPOP tablets without a top-coat ($f2$>70), at both 3% and 6% WG. This held true for all Opadry systems regardless of polymer chemistry (**Figure 3**). Top-coating to 6% WG was found to be more effectively masking the bilayer appearance of the PPOP tablets compared to 3% WG and hence is recommended for the Opadry systems evaluated in this study.

Figure 1. Comparison of PPOP Tablets with and without Top-Coat

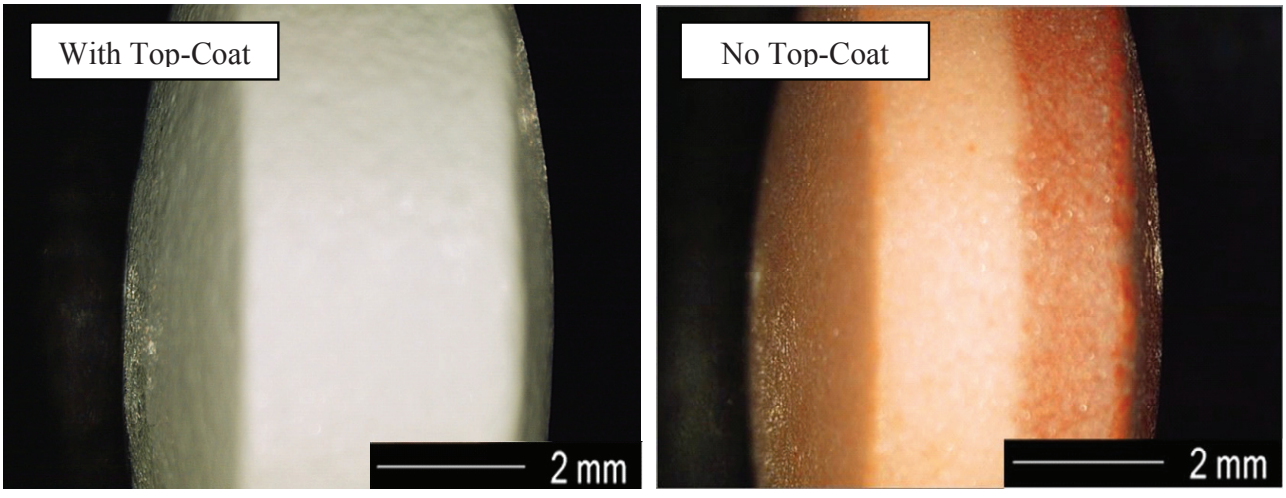
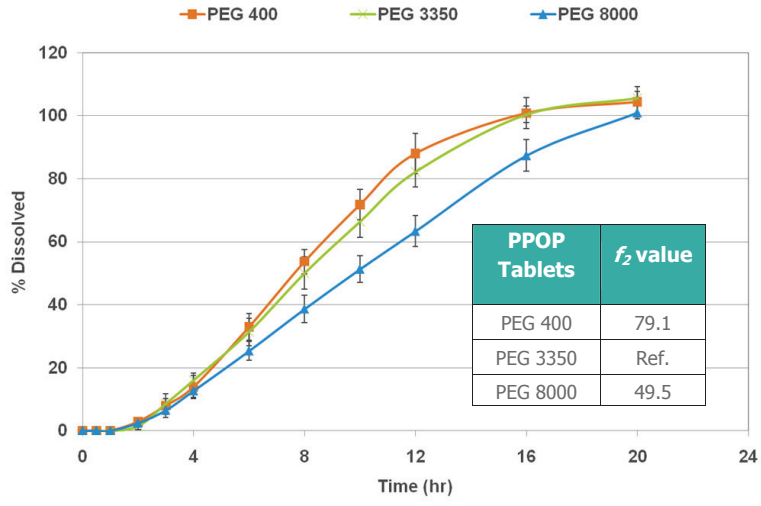
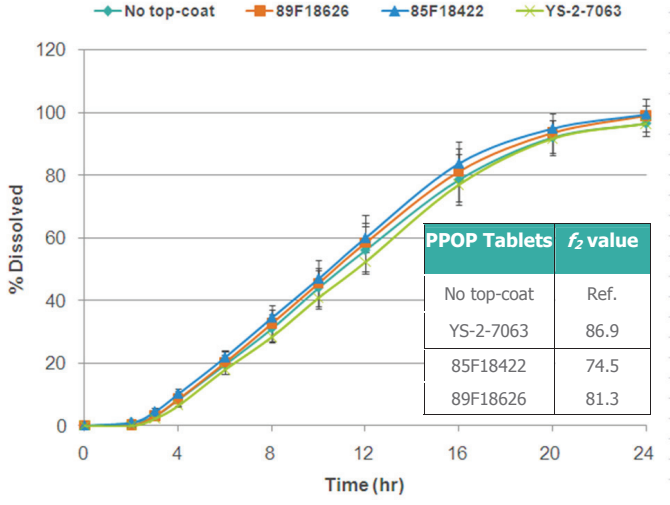


Figure 2. Release Profiles of Drug Y PPOP Tablets, Coated to 12% WG, using Semipermeable Membrane of Various PEG Grades (n=6)



PPOP Tablets	f_2 value
PEG 400	79.1
PEG 3350	Ref.
PEG 8000	49.5

Figure 3. Release Profiles of Drug Y PPOP Tablets, Top-coated with Various Opadry Systems to 6% WG (n=6)



PPOP Tablets	f_2 value
No top-coat	Ref.
YS-2-7063	86.9
85F18422	74.5
89F18626	81.3

Conclusions

PPOP tablets of a practically water insoluble model drug were successfully manufactured and evaluated using various PEG grades in the composition of the semipermeable membrane, and different Opadry film coating systems for top-coating. Results showed that the presence of PEG 8000 in the coating composition resulted in slightly slower drug release compared to PEG 400 and 3350. Application of Opadry systems at 6% weight gain did not significantly impact the drug release from PPOP tablets. These studies illustrate viable osmotic systems, the complexity of which can be readily managed by satisfactory development and manufacturing controls.

References

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